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微循环在阿尔茨海默病发生发展中的作用*

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摘要　微循环障碍是导致肌体局部组织或脏器功能降低的重要原因之一，与衰老、退行性变、免疫功能紊乱等多种疾病的发生发展密切相关．阿尔茨海默病患者中枢神经系统的能量代谢失调、缺血缺氧、代谢产物积累等均累及微循环．本文就甲醛和核糖代谢失调导致的微循环障碍与阿尔茨海默病的典型病理改变(Tau 蛋白过度磷酸化、β 淀粉样蛋白沉积及认知损伤)之间的关系进行了讨论．

关键词　微循环障碍，阿尔茨海默症，内源甲醛，内源核糖
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微循环是微动脉、微静脉、毛细血管和组织管道内的血液循环，是提供组织氧气、营养物质，传递能量，排除二氧化碳和代谢废物的基本结构和功能单位[1]．微循环障碍是指血液理化性质的改变，使管腔狭窄，血流速度减慢或血栓形成，使局部组织缺血缺氧，组织代谢机能混乱，严重时将导致组织死亡[2]．阿尔茨海默病(Alzheimer's diseases，AD)的发病因素与机制十分复杂，以细胞外 Aβ 形成的淀粉样沉淀和细胞内异常磷酸化 Tau蛋白形成的神经纤维缠结作为典型的病理改变[3-5]．在国内外开展的研究中，微循环障碍在 AD 发生发展中的作用得到了相当的重视[6]．因此，阐明微循环障碍在老年认知损伤中的机制，有助于 AD 的早期发现、预警、诊断、干预．

1　微循环障碍与 AD

伴随衰老，脑血流与脑脊液的流速降低，对葡萄糖与氧的代谢率也减慢[7]．经颅多普勒的检测，可以观察到脑老化，伴随脑灌注的降低[8-9]．PET、SPECT 或 CT 技术检测脑局部显示，血流量与脑脊液流速下降[10]．血流速度减低导致血液中的代谢物，如血糖、醛类[11]、胆固醇等残留在血液中，一些代谢产物在血管壁残留，形成血管狭窄．微循环障碍可直接导致脑供血不足，缺血缺氧．由于内环境代谢紊乱，代谢产物无法有效排除，造成有害物质的积累，使组织细胞受损或变性坏死[12]．微循环障碍还会引起脑内毛细血管数目降低，微血管扭曲、缠绕、扩张等超微结构的改变．最终导致脑组织病变的产生，引起阿尔茨海默症(表 1)[13]．

Hunter 等[12]发现，在 AD 患者脑内毛细血管的退化程度显著高于正常对照组，血管内皮细胞损伤并引起持续的炎症反应，可能是导致 AD 的原因．在早期的心外膜动脉粥样硬化病变中，冠状动脉的微血管的内皮依赖扩张反应已经失调，说明动脉粥样硬化可以影响到微循环系统[14]，同时动脉粥样硬化是 AD 的危险因素之一[15]．近期报道 AD 与机体慢性脱水相关，慢性脱水会导致脑部微血管内血小

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Table 1 The change of microcirculation in AD

表 1 AD 中微循环的改变

AD 症状	微循环改变	危险因素
情绪易激动、头痛、失眠或嗜睡、注意力不集中、记忆力衰退	脑部供血不足，脑组织无法得到充足氧气、营养物质，代谢产物不能充分排除	动脉粥样硬化、血压过高或过低、糖尿病、高血脂、肥胖等．另外，吸烟、过量饮酒、吃得过于油腻、运动少、喝水少等不良生活习惯也会影响微循环系统．
胸闷、气短、心悸	血流量减低，动脉炎症导致心肌供血不足	
手脚发凉、肢体麻木、偏瘫	肢体微血管狭窄和血流受阻，血液黏稠度增大	
视力模糊、听力下降、耳鸣	视网膜微循环受阻，耳内细胞组织缺血、缺氧造成细胞损伤	

板黏附性增加、血黏度增加、有毒代谢产物浓度升高等微循环障碍的发生．微循环失调会引起突触传递障碍[16-17]、脑网络损伤[18]、认知异常等类似阿尔茨海默病的症状[19-20]．因此，李婷等[21]提出的合理饮水，可能是改善微循环早期干预的有效方法之一．

Woodman 等[22]发现，胰岛素可以通过增加内皮依赖的一氧化氮合酶生成，从而扩张血管，增加器官的供血量．肥胖的 Zuker 鼠微血管胰岛素受体的磷酸化水平下降，血管舒张反应受损[23]．Lester 等[24]观察到 AD 患者脑内存在胰岛素抵抗，并将 AD 列为“3 型糖尿病”．

2 内源甲醛、氨基脲敏感的胺氧化酶与微循环

研究表明，微循环持续低灌注，主要由于白细胞黏附至微静脉壁、堵塞毛细血管以及白细胞与内皮细胞之间的高黏附力，导致微循环流速、流量降低．血管黏附因子包括细胞间黏附分子(intercellular cell adhesion molecule-1, ICAM-1)、选择素(selectin)与血管黏附蛋白 1 (vascular adhesion protein-1，VAP-1)等．表达在血管内皮细胞上的 VAP-1 既是一种黏附分子，又是一种酶，其可溶性形式为氨基脲敏感的胺氧化酶(semicarbazied- sensitive amine oxidases，SSAO)，溶于血液循环系统中，含有 Cu^{2+}，以 6 羟基多巴胺为辅酶，可以催化体内胺类物质，如甲胺、组胺和多胺等，在氧的参与下，产生醛类、过氧化氢和氨[25-26]．SSAO 也存在于血管内皮细胞，以膜结合形式存在，在炎症反应时血管内皮细胞表达量增加．VAP-1 参与白细胞越过血管内皮到组织过程中的滚动、黏附、渗出过程，影响白细胞浸润[27-28]．

氧化应激导致的脑损伤，是 AD 发生发展的重要学说．在应激情况下，会出现内源甲醛的升高，同时伴有 SSAO 的上调[29-30]．甲胺是其内源性底物之一，在体内催化脱氨基生成甲醛，同时产生过氧化氢和氨[31]．体内代谢产物如肾上腺素、肌酸、肌酸酐及胆碱的脱氨作用产生甲胺，在血液、尿液和组织中均存在甲胺[32]．甲胺在 SSAO 作用下产生的代谢产物甲醛导致血管内皮损伤和微循环功能失调[33]．甲醛与氨基酸的 ε 氨基作用形成羟甲基，可以与单胺、酰胺类物质作用生成希夫碱，形成亚甲基，也可以与一些重要生物分子如蛋白质、单链 DNA 形成不可逆的共价交联复合物，与血管壁膜蛋白产生不可逆的甲醛 - 蛋白质交联复合物，启动内皮损伤[34]．微循环代谢障碍中蓄积的甲醛可以自由透过细胞膜，导致神经系统慢性损伤、功能失调、认知障碍，从而导致神经系统退行性疾病，如阿尔茨海默病等[35-36]．聂春来等[37-38]用 0.5 mmo/L 甲醛处理小鼠神经母细胞瘤 N2a 细胞，2 h 后细胞出现皱缩、变圆的形态改变，细胞内 Tau 蛋白的 T181 位点与 S396 位点的磷酸化水平显著升高．同时，小鼠尾静脉注射甲醛后发现，小鼠脑内 Tau 蛋白也出现过度磷酸化的现象[39]．而 Tau 蛋白过度磷酸化，进一步形成神经纤维缠结是 AD 的标志性特征之一[40]．杨美凤等[41-42]发现，甲醇饲喂 3～5 岁猕猴，甲醇在体内经乙醇脱氢酶代谢产生甲醛，2～3 年后猕猴脑内出现 Aβ 淀粉样沉淀形成的老年斑，以及异常磷酸化 Tau 蛋白形成的神经纤维缠结(图 1)，同时猕猴出现了近期记忆障碍的近似老年痴呆的症状．临床试验也表明内源甲醛随老龄化进程而增加，尿甲醛浓度与痴呆的发病程度呈正相关[43-46]．

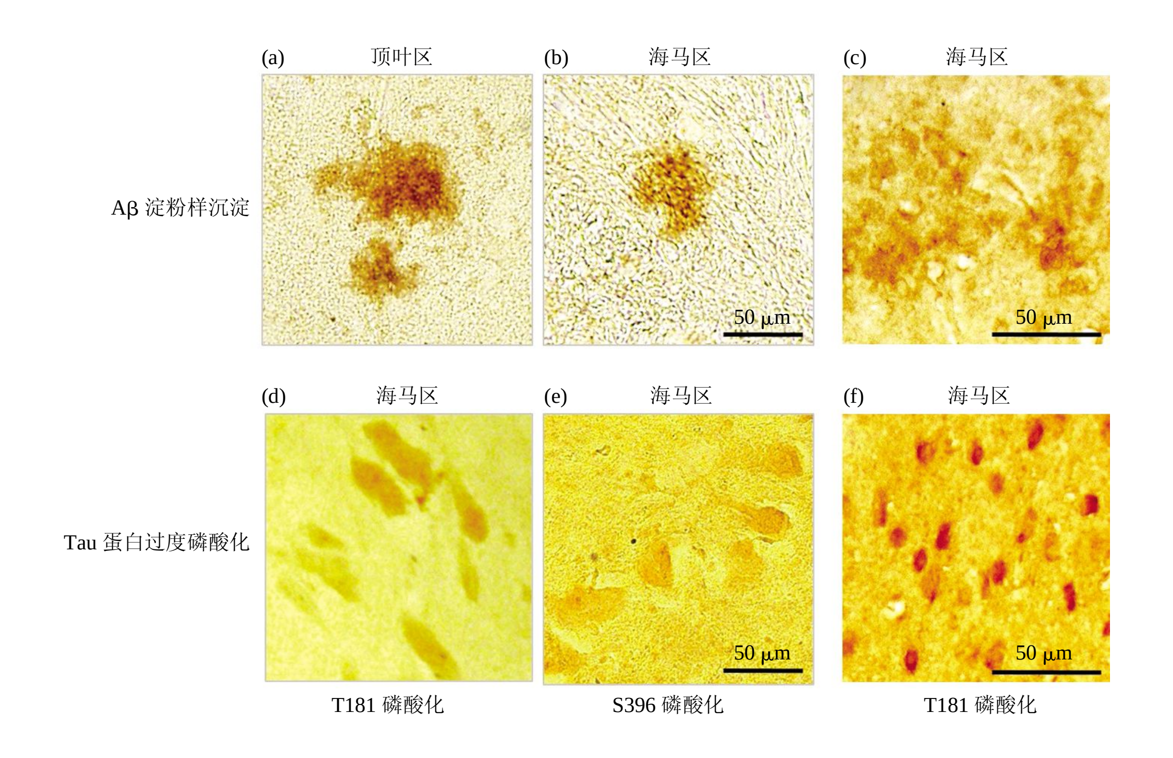


Fig. 1　Formaldehyde triggers abnormal modification of amyloid β and Tau protein

图 1　甲醛能够导致 Aβ 和 Tau 蛋白的异常修饰

5 岁的猕猴用低浓度甲醇处理 2 年，在脑部顶叶和海马区产生了老年斑(a, b)，Aβ 沉淀(c)，神经纤维样缠结(d, e, f)[41].

3　糖基化终末产物在微循环障碍中的作用

晚期糖基化终末产物(advanced glycosylation end products，AGEs)是还原糖与蛋白质 α、ε 氨基、精氨酸等发生的非酶糖基化产物，随着年龄的增长，在血清、组织中的积聚逐渐增加．AGEs 会使蛋白质交联，造成血管壁硬度增加，通过氧化应激、炎症等途径导致微循环障碍[47]．蛋白质的非酶促糖基化是血管基底膜增厚的主要原因[48-49]．微循环障碍表现在微血管基底膜增厚、内皮细胞增殖、血管腔狭窄和血管通透性增高．使神经中枢的星形胶质细胞发生形态与功能的变化，突触传递异常，神经元丧失．AGEs 的形成经三步：首先是还原糖的醛基与蛋白质的游离氨基反应形成希夫碱；继而形成可逆的早期糖基化产物；再经过 Amadori 分子重排，形成不可逆的糖基化终末产物[50]．AGEs 与内皮细胞特异性受体结合，产生活性氧自由基，诱导转录因子 NF-κB 活化，调控下游基因如黏附分子血管细胞黏附分子 1(VCAM-1)的表达，进一步促进血管内皮的损伤[51]．此外，血液中 AGEs 与内膜各种蛋白质结合或者自身交联，致使管腔狭窄、闭塞、血流变慢，甚至形成栓塞[52-53].

微循环障碍是糖尿病并发症发生发展的重要病理因素，糖尿病病人体内的 AGEs 显著升高[54]，其患阿尔茨海默病的概率比非糖尿病患者高 30%～65% [55]．用高 AGEs 饲喂小鼠，导致小鼠脑内 SIRT1 缺乏，β 淀粉样蛋白沉淀，出现类似 AD 的症状[56]．陈岚等[57-59]研究表明，核糖能够迅速与牛血清白蛋白(BSA)、神经 Tau 蛋白和突触核蛋白(α-synuclein)发生糖基化反应．虽然体内葡萄糖含量较高，但是核糖的糖基化能力显著强于葡萄糖[60]，糖尿病病人尿核糖显著高于正常人[61]．用核糖修饰的蛋白质与神经瘤母细胞(SH-SY5Y)共培养，表现出强烈的细胞毒性，核糖糖基化蛋白质与细胞膜上的 AGEs 受体(receptor for advanced glycation end products，RAGE)结合，开启下游途径如活性氧自

由基(ROS)、激活炎症反应、诱导细胞凋亡[62-63]. 韩婵帅等[64-65]观察到，给小鼠腹腔注射核糖后，小鼠血清与脑内蛋白质糖基化水平提高，提高脑内Tau蛋白过度磷酸化水平，海马星形胶质细胞激活，脑内出现炎症反应，小鼠空间延迟记忆受损(图2)，在这些病理过程中，也存在微循环障碍.

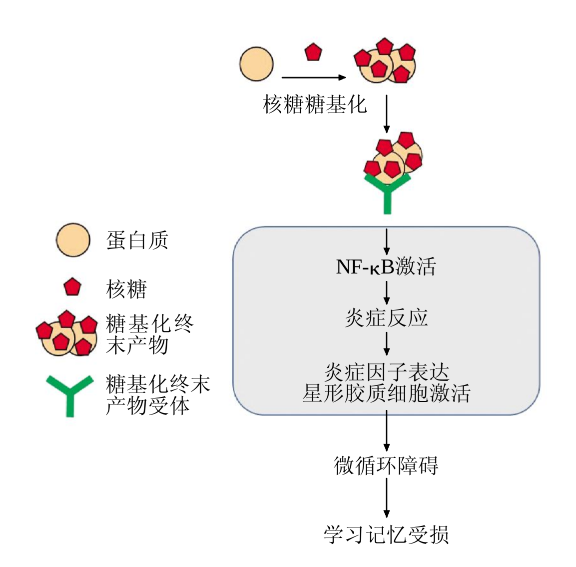


Fig. 2　Ribosylation inducing cognitive impairment through RAGE-dependent astrocytic inflammation and dysfunction of microcirculation

图2　核糖糖基化通过RAGE依赖的星形胶质细胞炎症和微循环障碍诱发认知损伤

星形胶质细胞和小鼠脑内AGE受体的升高与核糖诱导的AGE增多相关，导致RAGE依赖的NF-κB的激活，星形胶质细胞激活微循环发生障碍，进而导致空间学习与认知功能损伤[65].

4　小结与展望

影响脑部微循环障碍的因素很多，衰老、高血压、糖尿病及心脑血管疾病，使脑血流灌注减少，营养物质和氧气的供应不足，同时代谢产物不能及时清除，导致脑功能低下[66-68]. 脑内甲醛、核糖等代谢产物的过度积累，导致蛋白质异常修饰、错误折叠、分子聚集，从而损伤内皮细胞，出现微循环障碍[69]. 甲醛、核糖均可诱导神经Tau蛋白过度磷酸化、Aβ淀粉样沉积，以及认知损伤等类似阿尔茨海默病的症状[70-71]. 所以，有效清除蓄积的甲醛、核糖等代谢产物，是改善微循环障碍的有效手段之一. 作者在此建议，通过建立合理饮水、适当运动等生活方式，来减少体内微循环代谢产物的积累，增强和改善微循环功能.

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参 考 文 献

[1] Brown W R, Thore C R. Review: cerebral microvascular pathology in ageing and neurodegeneration. Neuropathol Appl Neurobiol, 2010, **37**(1): 56-74

[2] Craggs L J, Yamamoto Y, Deramecourt V, *et al*. Microvascular pathology and morphometrics of sporadic and hereditary small vessel diseases of the brain. Brain Pathol, 2014, **24**(5): 495-509

[3] Thal D R, Attems J, Ewers M. Spreading of amyloid, tau, and microvascular pathology in Alzheimer's disease: findings from neuropathological and neuroimaging studies. J Alzheimers Dis, 2014, **42**(Suppl 4): S421-429

[4] Kalaria R N. Neurodegenerative disease: Diabetes, microvascular pathology and Alzheimer disease. Nat Rev Neurol, 2009, **5** (6): 305-306

[5] Lu J, Li T, He R, *et al*. Visualizing the microtubule-associated protein tau in the nucleus. Sci China Life Sci, 2014, **57**(4): 422-431

[6] Farkas E, Luiten P G. Cerebral microvascular pathology in aging and Alzheimer's disease. Prog Neurobiol, 2001, **64**(6): 575-611

[7] Cullen K M, Kocsi Z, Stone J. Microvascular pathology in the aging human brain: evidence that senile plaques are sites of microhaemorrhages. Neurobiol Aging, 2006, **27**(12): 1786-1796

[8] Vriens E M, Kraaier V, Musbach M, *et al*. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. Ultrasound Med Biol, 1989, **15**(1): 1-8

[9] Brouwers P J, Vriens E M, Musbach M, *et al*. Transcranial pulsed Doppler measurements of blood flow velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy children and adolescents in relation to age and sex. Ultrasound Med Biol, 1990, **16**(1): 1-8

[10] Tachibana H, Meyer J S, Okayasu H, *et al*. Changing topographic patterns of human cerebral blood flow with age measured by xenon CT. AJR Am J Roentgenol, 1984, **142**(5): 1027-1034

[11] Chen J, Sun M, Wang X, *et al*. The herbal compound geniposide rescues formaldehyde-induced apoptosis in N2a neuroblastoma cells. Sci China Life Sci, 2014, **57**(4): 412-421

[12] Hunter J M, Kwan J, Malek-Ahmadi M, *et al*. Morphological and pathological evolution of the brain microcirculation in aging and Alzheimer's disease. PLoS One, 2012, **7**(5): e36893

[13] Perlmutter L S. Microvascular pathology and vascular basement membrane components in Alzheimer's disease. Mol Neurobiol, 1994, **9**(1-3): 33-40

[14] Panza J A. Coronary atherosclerosis: extending to the microcirculation? European Heart Journal, 2010, **31**(8): 905-907

[15] Fiolaki A, Tsamis K I, Milionis H J, *et al*. Atherosclerosis,

biomarkers of atherosclerosis and Alzheimer's disease. International Journal of Neuroscience, 2014, **124**(1): 1−11

[16] Nobutoki T, Ihara T. Early disruption of neurovascular units and microcirculatory dysfunction in the spinal cord in spinal muscular atrophy type Ⅰ. Med Hypotheses, 2015, **85**(6): 842−845

[17] Nguyen T H, Qiu X, Sun J, *et al*. Bulk endocytosis at neuronal synapses. Sci China Life Sci, 2014, **57**(4): 378−383

[18] Strobel C, Hunt S, Sullivan R, *et al*. Emotional regulation of pain: the role of noradrenaline in the amygdala. Sci China Life Sci, 2014, **57**(4): 384−390

[19] Jiang T. Brainnetome and related projects. Sci China Life Sci, 2014, **57**(4): 462−466

[20] 赵金辉, 叶　研, 陈华洁, 等. 北京地区部分居民饮水习惯调查及其影响因素分析. 环境与健康杂志, 2012, **29**(10): 942−944
Zhao J H, Ye Y, Chen H J, *et al*. Journal of Environment and Health, 2012, **29**(10): 942−944

[21] 李　婷, 强　敏, 赫荣乔. 慢性脱水与老年认知损伤及饮水干预. 神经药理学报, 2012, **2**(3): 43−51
Li T, Qiang M, He R Q. Acta Neuropharmacologica, 2012, **2**(3): 43−51

[22] Woodman R, Playford D, Croft K, *et al*. Basal production of nitric oxide is increased in the microcirculation in type 2 diabetes despite endothelial dysfunction: association with oxidative stress and blood pressure. Atherosclerosis Supplements, 2003, **4**(2): 307−308

[23] Woodman R J, Playford D A, Watts G F. Basal production of nitric oxide(NO) and non-NO vasodilators in the forearm microcirculation in type 2 diabetes: Associations with blood pressure and HDL cholesterol. Diabetes Research and Clinical Practice, 2006, **71**(1): 59−67

[24] Lester-Coll N, Rivera E J, Soscia S J, *et al*. Intracerebral streptozotocin model of type 3 diabetes: Relevance to sporadic Alzheimer's disease. Journal of Alzheimers Disease, 2006, **9**(1): 13−33

[25] Boomsma F, Hut H, Bagghoe U, *et al*. Semicarbazide-sensitive amine oxidase (SSAO): from cell to circulation. Med Sci Monit, 2005, **11**(4): RA122−126

[26] Obata T. Diabetes and semicarbazide-sensitive amine oxidase (SSAO) activity: a review. Life Sci, 2006, **79**(5): 417−422

[27] Mar Hernandez M, Esteban M, Szabo P, *et al*. Human plasma semicarbazide sensitive amine oxidase (SSAO), beta-amyloid protein and aging. Neurosci Lett, 2005, **384**(1−2): 183−187

[28] Somfai G M, Knippel B, Ruzicska E, *et al*. Soluble semicarbazide-sensitive amine oxidase (SSAO) activity is related to oxidative stress and subchronic inflammation in streptozotocin-induced diabetic rats. Neurochem Int, 2006, **48**(8): 746−752

[29] Gubisne-Haberle D, Hill W, Kazachkov M, *et al*. Protein cross-linkage induced by formaldehyde derived from semicarbazide-sensitive amine oxidase-mediated deamination of methylamine. J Pharmacol Exp Ther, 2004, **310**(3): 1125−1132

[30] Yu P H, Lu L X, Fan H, *et al*. Involvement of semicarbazide-sensitive amine oxidase-mediated deamination in lipopolysaccharide-induced pulmonary inflammation. Am J Pathol, 2006, **168**(3): 718−726

[31] Boor P J, Trent M B, Lyles G A, *et al*. Methylamine metabolism to formaldehyde by vascular semicarbazide-sensitive amine oxidase. Toxicology, 1992, **73**(3): 251−258

[32] Yu P H, Zuo D M. Formaldehyde produced endogenously *via* deamination of methylamine. A potential risk factor for initiation of endothelial injury. Atherosclerosis, 1996, **120**(1−2): 189−197

[33] Yu P H, Deng Y L. Endogenous formaldehyde as a potential factor of vulnerability of atherosclerosis: involvement of semicarbazide-sensitive amine oxidase-mediated methylamine turnover. Atherosclerosis, 1998, **140**(2): 357−363

[34] Su T, Monte W C, Hu X, *et al*. Formaldehyde as a trigger for protein aggregation and potential target for mitigation of age-related, progressive cognitive impairment. Curr Top Med Chem, 2015, **16**(5): 472−484

[35] Tong Z, Han C, Luo W, *et al*. Accumulated hippocampal formaldehyde induces age-dependent memory decline. Age (Dordr), 2012, **35**(3): 583−596

[36] 苏　涛, 宋　丹, 李　婷, 等. 核酸(脱)甲基化与内源甲醛及认知损伤. 生物化学与生物物理进展, 2015, **42**(3): 211−219
Su T, Song D, Li T, *et al*. Prog Biochem Biophys, 2015, **42**(3): 211−219

[37] Nie C L, Wang X S, Liu Y, *et al*. Amyloid-like aggregates of neuronal tau induced by formaldehyde promote apoptosis of neuronal cells. BMC Neurosci, 2007, **8**: 9 (DOI: 10.1186/1471-2202-8-9)

[38] Nie C L, Wei Y, Chen X, *et al*. Formaldehyde at low concentration induces protein tau into globular amyloid-like aggregates *in vitro* and *in vivo*. PLoS One, 2007, **2**(7): e629

[39] Lu J, Miao J, Su T, *et al*. Formaldehyde induces hyperphosphorylation and polymerization of Tau protein both *in vitro* and *in vivo*. Biochim Biophys Acta, 2013, **1830**(8): 4102−4116

[40] 魏　艳, 苗君叶, 刘　缨. 环境因素与 Tau 蛋白的异常磷酸化. 生物化学与生物物理进展, 2012, **39**(8): 778−784
Wei Y, Miao J Y, Liu Y. Prog Biochem Biophys, 2012, **39**(8): 778−784

[41] Yang M, Lu J, Miao J, *et al*. Alzheimer's disease and methanol toxicity (part 1): chronic methanol feeding led to memory impairments and tau hyperphosphorylation in mice. J Alzheimers Dis, 2014, **41**(4): 1117−1129

[42] Yang M, Miao J, Rizak J, *et al*. Alzheimer's disease and methanol toxicity (part 2): lessons from four rhesus macaques (Macaca mulatta) chronically fed methanol. J Alzheimers Dis, 2014, **41**(4): 1131−1147

[43] Tong Z, Han C, Luo W, *et al*. Aging-associated excess formaldehyde leads to spatial memory deficits. Sci Rep, 2013, **3**: 1807(DOI: 10.1038/srep01807)

[44] Yu J, Su T, Zhou T, *et al*. Uric formaldehyde levels are negatively correlated with cognitive abilities in healthy older adults. Neurosci Bull, 2014, **30**(2): 172−184

[45] Tong Z, Zhang J, Luo W, *et al*. Urine formaldehyde level is

inversely correlated to mini mental state examination scores in senile dementia. Neurobiol Aging, 2009, **32**(1): 31-41

[46] 苏 涛, 魏 艳, 赫荣乔. 改良 2, 4- 二硝基苯肼法测定脑内源甲醛. 生物化学与生物物理进展, 2011, **38**(12): 1171-1177
Su T, Wei Y, He R Q. Prog Biochem Biophys, 2011, **38** (12): 1171-1177

[47] Bonnardel-Phu E, Wautier J L, Schmidt a M, *et al*. Acute modulation of albumin microvascular leakage by advanced glycation end products in microcirculation of diabetic rats *in vivo*. Diabetes, 1999, **48**(10): 2052-2058

[48] Jaap a J, Tooke J E. Pathophysiology of microvascular disease in non-insulin-dependent diabetes. Clin Sci (Lond), 1995, **89**(1): 3-12

[49] Krentz a J, Clough G, Byrne C D. Interactions between microvascular and macrovascular disease in diabetes: pathophysiology and therapeutic implications. Diabetes Obes Metab, 2007, **9**(6): 781-791

[50] Wei Y, Han C S, Zhou J, *et al*. D-ribose in glycation and protein aggregation. Biochim Biophys Acta, 2012, **1820**(4): 488-494

[51] Wei Y, Han C, Wang Y, *et al*. Ribosylation triggering Alzheimer's disease-like Tau hyperphosphorylation *via* activation of CaMKII. Aging Cell, 2015, **14**(5): 754-763

[52] Peppa M, Uribarri J, Vlassara H. The role of advanced glycation end products in the development of atherosclerosis. Curr Diab Rep, 2004, **4**(1): 31-36

[53] Stirban A, Negrean M, Stratmann B, *et al*. Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. Diabetes Care, 2006, **29** (9): 2064-2071

[54] Singh R, Barden A, Mori T, *et al*. Advanced glycation end-products: a review. Diabetologia, 2001, **44**(2): 129-146

[55] Goh S Y, Cooper M E. Clinical review: The role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab, 2008, **93**(4): 1143-1152

[56] Cai W, Ramdas M, Zhu L, *et al*. Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. Proc Natl Acad Sci USA, 2012, **109**(39): 15888-15893

[57] Chen L, Wei Y, Wang X, *et al*. D-Ribosylated Tau forms globular aggregates with high cytotoxicity. Cell Mol Life Sci, 2009, **66**(15): 2559-2571

[58] Chen L, Wei Y, Wang X, *et al*. Ribosylation rapidly induces alpha-synuclein to form highly cytotoxic molten globules of advanced glycation end products. PLoS One, 2010, **5**(2): e9052

[59] Wei Y, Chen L, Chen J, *et al*. Rapid glycation with D-ribose induces globular amyloid-like aggregations of BSA with high cytotoxicity to SH-SY5Y cells. BMC Cell Biol, 2009, **10**: 10(DOI: 10. 1186/1471-2121-10-10)

[60] Su T, He R. D-ribose, an overlooked player in type 2 diabetes mellitus?. Sci China Life Sci, 2014, **57**(3): 361

[61] 苏 涛, 辛 亮, 赫英舸, 等. 2 型糖尿病患者尿核糖浓度显著高于正常. 生物化学与生物物理进展, 2013, **40**(9): 816-825
Su T, Xin L, He Y G, *et al*. Prog Biochem Biophys, 2013, **40**(9): 816-825

[62] Sousa M M, Yan S D, Stern D, *et al*. Interaction of the receptor for advanced glycation end products (RAGE) with transthyretin triggers nuclear transcription factor kB (NF-κB) activation. Lab Invest, 2000, **80**(7): 1101-1110

[63] Tobon-Velasco J C, Cuevas E, Torres-Ramos M A. Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. CNS Neurol Disord Drug Targets, 2014, **13**(9): 1615-1626

[64] Han C, Lu Y, Wei Y, *et al*. D-ribose induces cellular protein glycation and impairs mouse spatial cognition. PLoS One, 2011, **6**(9): e24623

[65] Han C, Lu Y, Wei Y, *et al*. D-ribosylation induces cognitive impairment through RAGE-dependent astrocytic inflammation. Cell Death Dis, 2014, **5**: e1117

[66] Kong a P, Chan J C. Hypoglycemia and comorbidities in type 2 diabetes. Curr Diab Rep, 2015, **15**(10): 646-652

[67] Mizutani K, Ikeda K, Tsuda K, *et al*. Inhibitor for advanced glycation end products formation attenuates hypertension and oxidative damage in genetic hypertensive rats. J Hypertens, 2002, **20**(8): 1607-1614

[68] Mcnulty M, Mahmud A, Feely J. Advanced glycation end-products and arterial stiffness in hypertension. Am J Hypertens, 2007, **20**(3): 242-247

[69] He R, Lu J, Miao J. Formaldehyde stress. Sci China Life Sci, 2010, **53**(12): 1399-1404

[70] Hua Q, He R. Alzheimer's disease - mechanisms, drug targets and alternative treatments. Curr Top Med Chem, 2016, **16**(5): 470-471

[71] Bartlett P F, He R. Introduction to the thematic issue "From brain function to therapy". Sci China Life Sci, 2014, **57**(4): 363-365

Microcirculation Dysfunction in Age-related Cognitive Impairment*

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Abstract Microcirculation dysfunction is regarded as one of important pathologies of senility, degeneration, immune disorder and many other diseases. Cerebral circulation insufficiency, energetic dysmetabolism, hypoxia-ischemia and metabolites accumulation in Alzheimer's disease (AD) have a close relation with microcirculation dysfunction. Here, we review microcirculation dysfunction playing an important role in hyperphosphorylation of Tau, Aβ aggregation and cognitive impairment induced by accumulation of formaldehyde and D-ribose.

Key words microcirculation dysfunction, Alzheimer's disease (AD), endogenous formaldehyde, endogenous D-ribose

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